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Cholesterol levels and cholesterol lowering in idiopathic dilated cardiomyopathy

We read with great interest the recent article of Dr Christ *et al.*[1] about the prognostic significance of serum cholesterol levels in patients with idiopathic dilated cardiomyopathy (IDC). It was found that decreased cholesterol levels do not independently predict adverse prognosis in patients with IDC and that low cholesterol levels are dependent on the severity of the disease (i.e. higher NYHA class, higher left ventricular end-diastolic diameter, and lower left ventricular ejection fraction). In contrast, the authors present an intriguing curve showing that, retrospectively, the prognosis (survival or transplant free survival) was significantly better for the few patients (~15%) who received statins at any time during follow-up. As stated in the discussion, beneficial effects of statins in heart failure patients indeed appear promising in some preliminary results, even in patients without coronary artery disease.[2] However, the particular analysis and results of Dr Christ may, in our opinion, be related to the fact that the patients who received statins were likely to be those with the highest cholesterol levels, i.e. those with the lower severity of the disease as suggested by the authors themselves. Therefore, it is really not sure that the better prognosis was related to the treatment with statins or to the lipid lowering. Prospective randomized intervention trials are thus particularly needed in the field.

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Cholesterol levels and cholesterol lowering in idiopathic dilated cardiomyopathy: reply

We greatly appreciate the comments of Fauchier *et al.* regarding our recently published findings.[1] Experimental and observational studies have raised concerns whether cholesterol lowering may adversely affect outcome in patients with chronic heart failure. We believe that those studies may not adequately address this clinically important issue due to (i) the artificial nature of those experimental studies and (ii) the mixed patient populations analysed including patients with coronary artery disease, which is an inflammatory disease by itself.

Owing to the exceptional opportunity in our institution, where patients with idiopathic dilated cardiomyopathy (iDCM) have been followed for several years (Marburg cardiomyopathy database), we have been able to examine aforementioned questions in a large cohort of iDCM patients, in whom systolic dysfunction due to other causes has been included on thorough examinations. Our data of this well-characterized patient group convincingly demonstrate that cholesterol levels depend on the severity of cardiac disease. Surprisingly, further analysis indicates that statins may beneficially affect outcome in iDCM patients supporting experimental and preliminary clinical findings in this field.[2,3] Although our data appear conclusive, they were derived from *post hoc* analysis with all limitations inherent with subgroup analysis. In addition, (i) a large number of patients on statins did not receive those drugs throughout the whole observational period; (ii) it cannot be excluded that iDCM patients with high cholesterol levels, which is associated with better outcome as already demonstrated in our study, are preferentially treated with statins leading to bias, although we have tried to adjust during statistical analysis. Subsequently, our data need to be confirmed by well-designed, prospective, randomized trials as suggested by Fauchier. Randomized clinical studies are already on the way to clarify this exciting concept (http://cvm.controlled-trials.com/content/2/6/266).

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Combined pharmacologic treatment with clopidogrel and statin for patients with acute coronary syndrome: is there a survival advantage?

We read with great interest the retrospective study by Lim *et al.*[1] on the impact of combined treatment of anti-platelet drugs and statin on the clinical outcomes of patients with acute coronary syndrome (ACS). The authors in their study suggest that despite the possibility of competitive drug interaction between statin and clopidogrel,[2] the combination of clopidogrel and statin has beneficial synergetic effects on the mortality of patients with non-ST-segment elevation ACS.

Randomized controlled trials over the past 20 years clearly show that aspirin, beta-blocker, ACE-inhibitor, and statin therapies prevent recurrent coronary events in patients with ACS.[3,4] In particular, statins have been associated with a substantial reduction of vascular morbidity and mortality. The benefits of statin therapy have been demonstrated in patients with coronary artery disease, hypertension, diabetes, and in those with elevated, averaged,[5] or even near-normal LDL-cholesterol levels.[6] Statins are known to promote an overall 24–37% reduction in the relative risk for coronary events, independent of other confounding variables such as age and sex (for review refer to Gotto[7]). Thus, statins are recommended in the current therapeutic guidelines for the treatment of ACS.[3,4]

Data provided by Lim *et al.*[1] show that the 6-month mortality estimated by the Kaplan–Meier curve was significantly lower in group IV (aspirin + clopidogrel + statin) compared with group II (aspirin + clopidogrel). We would like to make the following important notes: (1) the benefits of statins, beta-blockers, and ACE-inhibitors on the morbidity and mortality of patients with ACS have been well documented, (2) a statistically significant greater number of group IV patients compared with group II were on beta-blockers and ACE-inhibitors in the study conducted by Lim *et al.*,[1] and (3) *ex vivo* studies of clopidogrel and statin drug interactions show significant inhibition of clopidogrel metabolism but not statin efficacy.

Therefore, this suggests that the low mortality observed by Lim *et al.*[1] within group IV compared with group II could be simply attributed to the independent statin effect and/or to the effect of beta-blockers and ACE-inhibitors. The Lim *et al.*[1] study shows that statin significantly reduces the mortality in the 'treated' group IV compared with the 'non-treated' group II, and aspirin + clopidogrel could be considered as a background for both groups. In addition, the mortality rate of group III (aspirin + statin) and group II (aspirin + clopidogrel) were 3.6 and 4.4%, respectively. This further indicates the value of statin therapy in patients with ACS.

The Kaplan–Meier curve in the Lim *et al.*[1] study shows only the unadjusted mortality for group II vs. group IV. 'Restricting the main study comparisons to the two groups in whom clopidogrel was used', as stated by the authors, might not be sufficient to evaluate the synergistic effect of the drugs of interest on overall mortality. To investigate the additive and/or synergetic effect of clopidogrel and statin, Kaplan–Meier plot should include the adjusted mortality of all the four groups studied by Lim *et al.*

In conclusion, the retrospective study conducted by Lim *et al.*[1] in ACS patients makes it difficult to draw the conclusion that a 'clinically' superior effect exists for clopidogrel–statin drug combination. Moreover, the conclusion of additive or synergetic effects of the combined two drugs on the clinical outcomes of patients with ACS warrants further investigation.

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